the carbohydrate derivative is a biologically active molecule,

R is an alkyl or aromatic organic compound,

X is a binding group linking R to a protein that is bound to a biosensor surface.

46. The biosensor according to claim 22, wherein said spacer comprises albumin.

47. The biosensor according to claim 22, wherein said spacer comprises a protein.

48. The biosensor according to claim 25, wherein said signal transducer is a chemical transducer.

49. The biosensor according to claim 25, wherein said signal transducer is a physical transducer.

REMARKS

Applicant respectfully requests reconsideration of this application, as amended, and reconsideration of the Office Action dated February 11, 1999.

Claims 22-49 are pending in this application, as amended.

Claims 1-21 were rejected in the previous Office Action under 35 U.S.C. § 103(a) as being unpatentable over Nilsson, U.S. Pat. No. 4,918,009, in view of Attridge, WO 90/01166, and Karube, EP 0215669. Applicants respectfully traverse this rejection and request its withdrawal. Because claims 1-21 have been canceled from the application, the rejection of those claims is now moot. Applicants respectfully submit that new claims 22-49 are free of the art cited.

The invention as presently claimed comprises an immobilized carbohydrate derivative biosensor having a surface, a spacer molecule bound to the surface, and a carbohydrate derivative glycosidically bound to the spacer molecule. The carbohydrate derivative, as further described in the same claim, specifically binds to a portion of a protein, a virus or a cell in a sample.

Support for the spacer molecule is found in the specification, for example, at page 4, last full paragraph. The spacer molecule is a further improvement over the prior art, providing such cited benefits as avoidance of steric hindrance in binding to the carbohydrate derivative, id., for example as the number of binding sites becomes exhausted. The spacer molecule also allows the invention to be optimized so that only the biologically active portion of the carbohydrate derivative need be provided on the biosensor. In other words, with a spacer molecule attaching the carbohydrate derivative to the surface, one can focus on the biologically active part of the carbohydrate derivative, which as taught at page 3, second paragraph of the specification is "sufficient for the oligosaccharide to bind a protein, virus or a cell in a biospecific manner." The ability to use only the biologically active part would also increase the specificity of the desired coupling of the carbohydrate derivative with the target molecule to be detected, as any non-specific binding to other areas of the carbohydrate derivative might easily be avoided.

The carbohydrate is further described, in claim 23, as being a biologically active part of a naturally occurring carbohydrate sequence which binds in a biospecific manner to target portions of the biological sample. Support for this description is found, for example, at page 3, paragraph 2, of the specification.

The Advisory Action asserted that the Applicant's earlier (Nilsson) patent, as the primary document on which the obviousness rejection was based, discloses carbohydrate derivatives according to the claimed invention. The Advisory Action asserted that Nilsson teaches coupling

the carbohydrate derivatives to proteins or lipids, or to solid carriers. The Action then asserted that Attridge et al. "teach the use of [a] sensor to immobilize a carbohydrate," and that one skilled in the art would have had a reasonable expectation of success in immobilizing the carbohydrates of Nilsson on the biosensor of Attridge et al. because "the solid carriers of Nilsson et al. is seen to be functionally equivalent to the solid sensor of Attridge et al." Applicants respectfully disagree with this characterization.

The earlier (Nilsson) patent, rather than particularly disclosing carbohydrate derivatives according to the claimed invention, as the Action suggests, instead teaches a method of controlling the regioselectivity of glycosidic bonds, see Abstract of the Invention, using enzymes, "nature's own catalysts," to overcome the lack of specificity in traditional organic synthesis of carbohydrates, column 2, lines 13-52. Nilsson thus does not teach a method of carbohydrate derivatives synthesis, but rather, a method of selective synthesis of carbohydrates.

The earlier Nilsson patent does mention that people were at that time "working intensely" to develop oligosaccharides for use in "novel diagnostics," but there is no further mention in that document of how such diagnostics might be prepared, for what such diagnostics might be used, or of what materials such diagnostics might be comprised. The reference to "novel diagnostics" was no doubt intended simply to teach the direction in which such research in the area was to be carried out in the future, not to prevent later obtaining protection for advances not even considered at the time the document was filed.

Applicants note that traditional diagnostics ordinarily comprise several compounds, of either biochemical or synthetic origin, or mixtures of both, by which a biologic effect is indicated indirectly, typically through several reactions occurring in succession, the end result often being a non-specific color change unrelated to the initial biochemical to be detected. There is certainly no

indication in that document that direct monitoring of biomolecular interaction, as in the claimed invention, is even possible, much less how such a result might be obtained.

Further, there is no reason set forth in that document, and none from the document has been cited by the Examiner, to indicate *why* one might want to immobilize the compounds according to that document to solid carriers. There is certainly nothing to suggest binding to a surface as in the claimed invention, using a spacer molecule, for any reason whatever. There is no reason taught in that document to immobilize such compounds on a solid surface, and no function disclosed for such immobilized compounds. In other words, there is no function set forth in Nilsson for immobilized carbohydrates. And yet, the Advisory Action asserted that "the solid carriers of Nilsson et al. is seen to be functionally equivalent to the solid sensor of Attridge et al.", and so presumably, that of the claimed invention. Applicants respectfully submit that this is pure speculation, and is incorrect as a matter of fact.

The claimed invention provides a carbohydrate derivative attached to a surface with a spacer molecule in order to facilitate binding of the target molecule to the carbohydrate derivative of the biosensor. This is a further optimization of a unique structure. The claimed invention also provides that the carbohydrate derivative specifically binds to a portion of a protein, a virus or a cell in a sample. Applicants emphatically assert that the solid carrier of the earlier (Nilsson) patent is not functionally equivalent to either Attridge or to the claimed invention. Applicants submit that it cannot be determined to what the solid carrier of that earlier patent might be functionally equivalent, since no function is taught in that document, but that the carrier in Nilsson is clearly structurally different from the claimed invention. Because the present invention is claimed based on its structure, that difference in structure provides patentability.

Attridge, et al., as a secondary reference on which the obviousness rejection was based, was cited as teaching an immobilized ligand, and as teaching that the ligand could be a specific carbohydrate. The Office Action of April 29, 1996 admitted, however, that "Attridge et al. do not teach the specific carbohydrate derivatives recited in the instant claims." Page 5, at paragraph 9 of that Office Action. Applicants further submit that, as discussed in reference to the Nilsson patent above, not only does Attridge not teach the carbohydrate derivatives of the claimed invention, Attridge does not teach the spacer molecule portion of the claimed invention either. As the spacer molecule, and indeed the biologically active carbohydrate derivative of the claimed invention, are neither taught nor suggested by Attridge, the deficiencies of the earlier Nilsson reference are not overcome by Attridge et al.

Applicants respectfully submit that the other secondary reference, Karube, likewise does not address the deficiencies of the earlier Nilsson reference. Karube teaches at page 6, lines 15-28 that:

> An adsorbent receptor, such as selected from among enzymes, sugars, lipids, co-enzymes, amino acids and proteins such as lectins, antibodies or protein A, is immobilized on the surface of the piezoelectric crystal of a biosensor. A sample to be analysed is adsorbed by the receptor. Then the constituents of the sample are eluted with eluents slightly differing in pH value or ionic strength from each other or containing organic solvents. Thus the presence and amount of each constituent can be determined from the resonant frequency of the piezoelectric crystal biosensor before and after elution.

Simply mentioning "sugars" broadly in a list of potential biochemicals which might prove useful in such measuring devices does not remedy the deficiencies of the earlier Nilsson reference. It has already been noted that some of the deficiencies in that document result from the lack of a spacer molecule, which in turn allows steric hindrance and the potential for reduced specificity, due to a larger portion of the carbohydrate derivative being necessary to attach the molecule to the surface of the biosensor than is required to obtain biospecific binding.

Thus we see that Karube suffers from the same deficiency which the Applicants have overcome, namely, non-specific binding at the biomolecule attached to the biosensor. As Karube explains, this results in several molecules attaching to the biomolecule, which then have to be separated from the target molecule. Instead of remedying the problem by optimizing the biologically active biosensor surface, Karube overcomes the problem by separating the several molecules which become non-specifically attached to the biomolecule of the biosensor by elution. This is a much more tedious and time-consuming process than simply exposing the biosensor to a sample and obtaining specific binding of the target molecule.

Clearly nothing in Karube teaches overcoming the specificity problems by optimizing the biologically active portion through attachment to a spacer molecule. Karube solves the deficiency by a less desirable solution, teaching away from Applicants' solution to the known problem in the art. Because Karube is not seen to remedy the deficiencies of the earlier Nilsson reference, Applicants respectfully submit that the Examiner's rejection is overcome.

Applicants respectfully submit that the all of the objections and rejections presently pending in the application are overcome. Applicants therefore respectfully request that the rejections be withdrawn, and that the claims be allowed at the Examiner's earliest convenience.

If any additional fees are due in connection with the filing of this Amendment, such as additional fees under 37 C.F.R. §§ 1.16 or 1.17, please charge the fees to our Deposit Account No. 02-4300. If an additional extension of time under 37 C.F.R. § 1.136 is necessary and not accounted for in the papers filed herewith, such an extension is requested. The extension fee should also be charged to Deposit Account No. 02-4300. Similarly, any credit due should be credited to Deposit Account No. 02-4300.

Respectfully submitted,

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